REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-15 and 18-26 are pending in the application subsequent to entry of this Amendment. In this Amendment claim 1 has been amended to specify in more detail the nature of the additive(s) included in the composition; *see* in particular the additives specified in claims 13 and 14. The additive may also be a mixture of the two components specified as was indicated in claim 1 prior to amendment.

Claim 16 has been replaced by new method claim 26 and relates to the composition of amended claim 1. Consequential changes with respect to claims 18-23 are made; claim 17 has been deleted to reduce issues.

As a preliminary matter, this application entered the United States via the Patent Cooperation Treaty and is a national phase under 35 USC §371 of PCT/GB04/01651. Included in the application are documents acknowledged in the Notice of Acceptance of Application mailed February 16, 2006 (copy attached) and among them acknowledgement of the priority document is included. However, item 12 of the current Official Action makes no mention of receipt of applicants' claim for benefit of priority or receipt of a certified copy of the priority document during the national stage from the International Bureau; *see* item 12(a)(3). In the next communication the examiner is requested to acknowledge the priority claim and receipt of the certified copy.

Items 2-5 of the Official Action are directed to the format of claims 16-23. Appropriate method terminology has been employed thus these objections are no longer relevant.

The balance of the Official Action deals with various prior art-based rejections of selected claims the primary reference being the published U.S. application of Soltero et al; *see* items 9-18 of the Action. Applicants respond to these rejections as follows:

Soltero *et al*

Soltero *et al* describe pharmaceutical compositions that include a drug-oligomer conjugate, a fatty acid component, and a bile salt component (see, for example, the abstract).

The Examiner suggests that methyl- and propyl hydroxybenzoate, which are mentioned by Soltero *et al* as preserving agents that can be added to their compositions, fall within the definition of the additive of claim 1. As discussed below, the benzoate derivatives Soltero *et al* are referring to do not fall within the scope of the additive defined in amended claim 1.

Amended claim 1 is therefore novel over Soltero *et al.*

At paragraph [0228] Soltero *et al* have indicated it is possible to add "preserving agents such as methyl- and propyl hydroxybenzoates;...". The Examiner asserts that this includes propyl gallate. With respect, the applicant disagrees. Propyl gallate is not a preserving agent; rather, it is an antioxidant.

As the Examiner will be aware, there are fundamental differences in the properties of preservatives compared to antioxidants. Preservatives retard spoilage resulting from e.g. microbial growth. Antioxidants, on the other hand, specifically reduce the rate of particular oxidation reactions and the consumption of oxygen. These differences are reflected in, for example, the categories used in the International Numbering System (INS) for food additives determined by the Codex Alimentarius committee. Certain countries, particularly in Europe, prefix the INS number by an "E" to designate those INS additives that they have approved for use.

According to the INS food additives numbered in the range 200 to 299 specifically denote compounds which are preservatives. Thus, the compounds envisaged by Soltero *et al* in this reference are clearly the known preservatives methyl *para*-hydroxybenzoate (food additive number 218, a.k.a. "E218") and propyl *para*-hydroxybenzoate (food additive 216, a.k.a. "E216"). An INS food additive number of 300 to 399, on the other hand, specifically denotes a compound which is an antioxidant and/or an acidity regulator. Thus, this different class of food additive is distinguished exclusively from the class of preservatives. Propyl gallate, being an antioxidant and not a preservative, has a food additive number of 310 (a.k.a. "E310"). Accordingly, there is no disclosure in Soltero *et al* of propyl gallate. Thus, as noted above, claim 1 is novel over Soltero *et al.*

Claim 1 is also inventive over Soltero *et al.* In particular, there is no teaching in Soltero *et al* which would lead one to combine an additive as defined in amended claim 1 to the compositions they describe. Paragraph [0228] of Soltero *et al* provides a lengthy "laundry list" of "suitable excipients" that could be used with their compositions. As noted above, methyl *para*-hydroxybenzoate and propyl *para*-hydroxybenzoate are indicated in this list. However, no compound falling within the definition of the additive of new claim 1 is indicated. Thus, there is no suggestion whatsoever that might lead a skilled person to a composition falling within

amended claim 1.

Moreover, in view of Soltero *et al* the fact that the additive of amended claim 1 advantageously enhances the solubility of bile salts is wholly unexpected. Incidentally, any skilled person seeking to enhance the solubility of bile salts would have no reason to contemplate using the preservatives methyl *para*-hydroxybenzoate and/or propyl *para*-hydroxybenzoate (which are not even covered by the definition of the additive of new claim 1). Accordingly, the composition as defined in claim 1 is not obvious from Soltero *et al.*

As all of the remaining claims are dependent on claim 1, they must also be novel and inventive over Soltero *et al.*

Soltero *et al* and Lacy *et al*

Lacy *et al* describe carriers for hydrophobic drugs, which carriers comprise a digestible oil and a pharmaceutically acceptable surfactant component for dispersing the oil *in vivo* when the carriers are administered (see, for example, the abstract).

The Examiner asserts that it would be obvious to combine the teachings of these two documents and arrive at a composition of claim 1. With respect, the applicant disagrees.

The Examiner notes that butyl hydroxyanisole and propyl gallate may be added to the compositions disclosed in Lacy *et al.* However, in fact, this section of Lacy *et al* appears to be merely incidental to the document's teaching. This is because these two additives are mentioned simply as "optional ingredients" (see column 13, line 58). They are just two of a "laundry list" of further optional ingredients, wide-ranging in properties, which list starts at column 13 line 58 and finishes at column 14 line 3. Lacy *et al* indicate no purpose or advantage associated with the addition of any of these ingredients beyond their normal known properties. In the case of butyl hydroxyanisole and propyl gallate, this property is that of being an antioxidant. Thus, there is no suggestion whatsoever of any advantageous property of either of these additives beyond that which was already known.

The Examiner suggests that it would be obvious to add these ingredients to the compositions of Soltero *et al.* However, this is not so, because these two components appear not to be compatible on the basis of Soltero *et al.* As noted above, in paragraph [0228] Soltero *et al* lists a large number of excipients said to be suitable for adding to the compositions it describes. This list includes lubricating agents, wetting agents, binding agents, anticaking agents,

preserving agents, sweetening agents, flavoring agents, polyols, inert fillers, bulking agents and granulating agents. This list does not, however, include antioxidants.

Moreover, Lacy *et al* are concerned with a different problem to that addressed by the present invention. The "real" teaching of Lacy *et al* is alluded to at column 3, lines 14-25. They have discovered (i) that the lipolysis of fatty oil in the gastroinstestinal tract can enhance the dissolution rate of a hydrophobic drug administered with the fatty oil, (ii) that this beneficial lipolysis is actually retarded by surfactants conventionally used in hydrophobic drug formulations, and (iii) that this retarding effect can be reduced by selecting certain lipophilic co-surfactants. Based on this, Lacy *et al* describe the use of a digestible oil in conjunction with a surfactant as a carrier for hydrophilic drugs (see, for example, column 3 lines 38-4). Thus, Lacy *et al* are concerned with enhancing the solubility of the drug (which corresponds to the active principal of claim 1 of the present invention). The present invention, however, concerns enhancement of the solubility of the bile salt. Lacy *et al* would therefore be of no assistance whatsoever to a skilled person, starting from Solero *et al*, seeking to enhance the solubility of the bile salt.

Accordingly, the present invention is not obvious over Soltero *et al* and Lacy *et al*.

Soltero *et al* and Bradley

Bradley describes a new class of anti-diabetic drugs (glitazones) that act by improving sensitivity to insulin (see, for example, page 191, second paragraph).

The Examiner argues that Bradley discloses the features of dependent claim 11, because glitazone is an insulin sensitizing drug. He suggests that it would have been obvious to take an insulin-containing composition described by Soltero *et al* (said to fall within claim 1) and add to it a glitazone (as described in Bradley) to arrive at a composition falling within claim 11. However, this objection relies on the assumption that Soltero *et al* disclose an additive as defined in claim 1. As discussed above, this is not so. Accordingly, this objection is no longer relevant.

Soltero *et al*, New and Russell-Jones

New describes compositions containing a bile salt and a buffer (such as a carbonate or bicarbonate salt) which is adapted to buffer the gut to a pH of from 7.5 to 9, which compositions can increase bioavailability of an active molecule (see abstract). Russell-Jones describes substances for oral administration which are "coated" or "encapsulated" with a carboxylic acid to

protect against proteolysis in the stomach (see abstract).

The Examiner suggests that New and Russell-Jones disclose the features of dependent claim 3 and argues it would have been obvious to apply this to a composition of Soltero *et al.* However, this objection also relies on the assumption that Soltero *et al* disclose an additive as defined in claim 1, and accordingly is also no longer relevant.

Soltero *et al*, Strickley *et al* and Harsch *et al*

Strickely *et al* describe studies showing that the effects of residual moisture on solid-state reactions with Human Insulin II depend critically on nature of the reaction under consideration (see, for example, the Conclusions section on page 652). Harsch *et al* is a review article summarizing the evolution of insulin therapy (see title).

Again, the Examiner argues that the features of dependent claims (2 and 22) are disclosed by Strickley *et al.* As before, though, this is reliant on the assumption that Soltero *et al* disclose a composition of claim 1, which it does not. Accordingly, this objection no longer applies.

Notwithstanding this, the applicant wishes to draw the Examiner's attention to the fact that Harsch *et al* are concerned with a dry-powder insulin formulation for delivery via the lungs (see, for example the summary, lines 3-6). The present invention, on the other hand, concerns compositions which offer advantageous effects when used for oral administration, and a skilled person would not expect that such a solid powder could be used in oral administration because the stomach and intestine are essentially aqueous environments.

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited. Should the examiner require further information please contact the undersigned.

Respectfully submitted,

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